PYRIMIDINE NUCLEOSIDES OF THE FURANOSE FORM OF 2-AMINO-2-DEOXY-D-GLUCOSE*

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ABSTRACT

Partial demercaptalation of 2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal yielded ethyl 2-deoxy-1-thio-2-(trifluoroacetamido)-α-D-glucofuranoside (**2**). This compound was also prepared by deacetylation of ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside followed by treatment of the product with *S*-ethyl trifluorothioacetate. Acetylation of **2**, followed by treatment with chlorine, gave 3,5,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-D-glucofuranosyl chloride (**6**), which was condensed with bis(trimethylsilyl)cytosine to give 1-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucofuranosyl]cytosine (**7**). Compound **7** was deacylated with methanolic ammonia to give 1-(2-amino-2-deoxy-β-D-glucofuranosyl)cytosine, isolated as the sulfate. Condensation of **6** with bis(trimethylsilyl)-thymine yielded 1-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucofuranosyl]thymine, which was deacylated with methanolic ammonia to give 1-(2-amino-2-deoxy-β-D-glucofuranosyl)thymine, isolated as the hydrochloride.

INTRODUCTION

The synthesis of nucleosides of 2-amino-2-deoxy sugars, preferably in their furanose form, has long been of interest in this laboratory. To date, the only nucleosides of the furanose form of a 2-amino-2-deoxyhexose to be synthesized are the anomeric 9-(2-amino-2-deoxy-D-glucofuranosyl)adenines[1]. We now report the synthesis of two pyrimidine nucleosides of the furanose form of 2-amino-2-deoxy-D-glucose, namely, 1-(2-amino-2-deoxy-β-D-glucofuranosyl)cytosine and 1-(2-amino-2-deoxy-β-D-glucofuranosyl)thymine.

Initially, it was necessary to obtain a suitable derivative of 2-amino-2-deoxy-D-glucose in the furanose form. The ethyl 1-thioglycofuranosides, which may be obtained directly by demercaptalation of a sugar diethyl dithioacetal, are useful for this type of synthesis[2], especially because the 1-(ethylthio) group may (after protection

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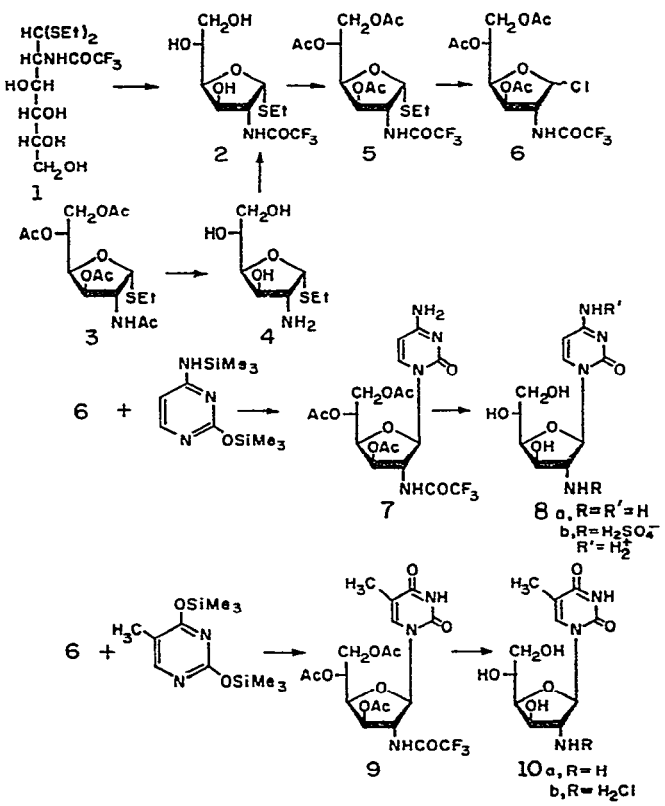
of the hydroxyl groups) be replaced by halogen to give a glycofuranosyl halide. Wolfrom and co-workers[3] first applied the demercaptalation procedure to the synthesis of an ethyl 1-thioglycofuranoside of a 2-amino-2-deoxy sugar; by partial demercaptalation of 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal, they obtained ethyl 2-acetamido-2-deoxy-1-thio-α-D-glucofuranoside and the corresponding β-D anomer (as the triacetate). Their procedure was modified by Wolfrom and Winkley[4] to give the α-D anomer in high yield. Wolfrom and Winkley[1] employed ethyl 2-deoxy-2-(2,4-dinitroanilino)-1-thio-α-D-glucofuranoside for the synthesis of the anomeric 9-(2-amino-2-deoxy-D-glucofuranosyl)adenines. The 1-thiogluco-furanoside was acetylated, and the acetate was treated with chlorine to give the protected glucofuranosyl chloride; this was condensed with 6-acetamido-9-chloro-mercuripurine to give the anomers of the protected nucleosides. For the present work, a similar procedure was employed, by use of a suitably protected 1-thiogluco-furanoside, but with trifluoroacetyl as the amino-protecting group.

DISCUSSION

The first consideration was the synthesis of a 2-amino-2-deoxy-1-thiogluco-



furanoside having the *N*-trifluoroacetyl protecting group. Two alternative routes to this type of derivative were investigated. The first involved introduction of the *N*-trifluoroacetyl group before demercaptalation of a sugar diethyl dithioacetal, and the second involved introduction of this group after the demercaptalation. Partial demercaptalation of 2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal[5] (**1**) with aqueous mercuric chloride in the presence of mercuric oxide gave crystalline ethyl 2-deoxy-1-thio-2-(trifluoroacetamido)-α-D-glucofuranoside (**2**) in 37% yield. Compound **2** was also prepared, in 70% yield, from ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside (**3**) by deacetylation with refluxing aqueous barium hydroxide, followed by treatment of the product (**4**) with *S*-ethyl trifluorothioacetate. Acetylation of **2** with acetic anhydride–pyridine yielded crystalline ethyl 3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-2-(trifluoroacetamido)-α-D-glucofuranoside (**5**) in 91% yield.

Treatment of a solution of **5** in dichloromethane with chlorine gave syrupy 3,5,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-D-glucofuranosyl chloride (**6**), which was immediately condensed with bis(trimethylsilyl)cytosine[6,7] by the fusion technique[6,8]. Crystallization of the crude product gave 1-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucofuranosyl]cytosine (**7**) in 12% yield; an additional 2.3% of crystalline **7** was isolated from the mother liquor by preparative t.l.c. Attempted isolation of a second (anomeric) nucleoside derivative from this mother liquor was unsuccessful. The protected nucleoside (**7**) was deacylated with methanolic ammonia at room temperature, to give amorphous 1-(2-amino-2-deoxy-β-D-glucofuranosyl)cytosine (**8a**), which was immediately converted into the crystalline sulfate **8b**, obtained in 85% yield from **7**. The anomeric assignments of **7** and **8** were made on the basis of optical rotatory dispersion (o.r.d.). The o.r.d. spectrum of **8b** in water

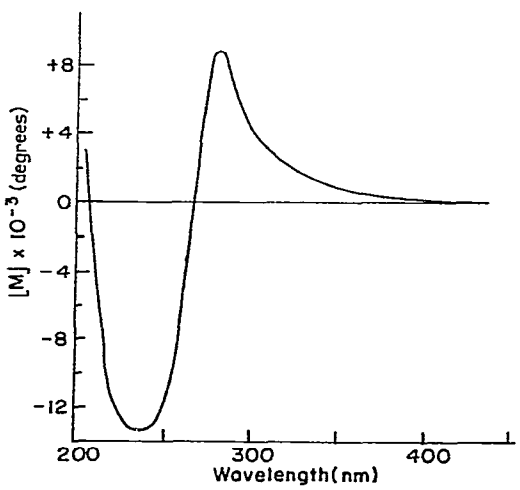


Fig. 1. Optical rotatory dispersion spectrum of 1-(2-amino-2-deoxy-β-D-glucofuranosyl)cytosine sulfate (**8b**).

(see Fig. 1) exhibited a positive Cotton effect. A positive Cotton effect has been found[9–11] characteristic of the β-D configuration in pyrimidine nucleosides of the furanose form.

Condensation of **6**, freshly prepared from **5**, with bis(trimethylsilyl)thymine[6,7] by the fusion technique[6,8] gave crystalline 1-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucofuranosyl]thymine (**9**) in 52% yield from **5**. Compound **9** was deacylated with methanolic ammonia, and the crude product (**10a**) was immediately converted into the crystalline hydrochloride (**10b**), obtained in 83% yield from **9**. The anomeric assignments for **9** and **10** were made on the basis of the o.r.d. spectrum

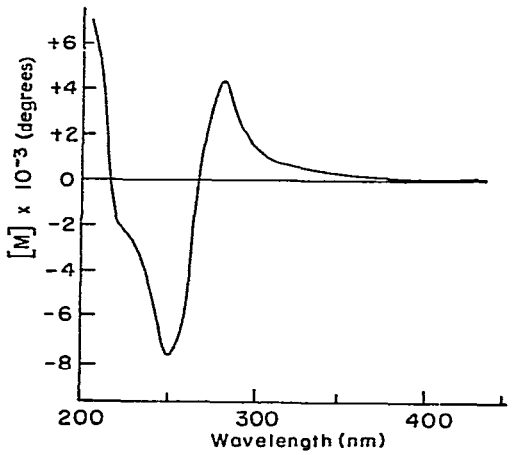


Fig. 2. Optical rotatory dispersion spectrum of 1-(2-amino-2-deoxy-β-D-glucofuranosyl)thymine hydrochloride (**10b**).

of **10b** (see Fig. 2). This spectrum (measured in water) exhibited a positive Cotton effect, characteristic[9–11] of the β-D configuration of pyrimidine nucleosides of the furanose form.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover apparatus. Specific rotations were determined with a 2-dm polarimeter tube. Infrared spectra were recorded with a Perkin–Elmer Infracord spectrometer. Ultraviolet spectra were recorded with a Bausch and Lomb Spectronic 505 spectrometer. O.r.d. spectra were recorded with a Jasco ORD/UV5 spectrometer. X-Ray powder diffraction data give interplanar spacings (Å) for CuKα radiation. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The stronger lines are numbered (1, strongest); multiple numbers indicate approximately equal intensities. T.l.c. was performed with Desaga equipment by using Silica Gel G (E. Merck, Darmstadt, Germany), activated at 110°. Indication was effected by sulfuric and,

unless otherwise noted, proportions for developers are given by volume. Microanalyses were made by W. N. Rond. Evaporations were performed under diminished pressure (water aspirator).

Ethyl 2-deoxy-1-thio-2-(trifluoroacetamido)-α-D-glucofuranoside (**2**). — *Method A.* To a suspension of mercuric oxide, freshly prepared from mercuric chloride (2.7 g) by the method of Pacsu and Wilson[2], in water (30 ml) was added 2-deoxy-2-(trifluoroacetamido)-D-glucose diethyl dithioacetal[5] (**1**, 2.8 g). Mercuric chloride (1.1 g) in water (50 ml) was added to the stirred suspension during 2 h, and stirring was continued for 30 min after completion of the addition. The mixture was then filtered through a pad of Celite, and the filter cake was washed with water (20 ml). The filtrate and washings were combined, and evaporated to a syrup that was dried by repeated addition and evaporation of ethanol. T.l.c. of the resulting syrup with 20:1 ethyl acetate–methanol as the developer revealed a major component (R_F 0.64) and three minor components (R_F 0.59, 0.25, and 0.10). The component having R_F 0.59 corresponded to the starting material (**1**). The crude product was heated for 1 h in refluxing toluene, and evaporation of the solvent gave a solid residue (2.3 g). T.l.c. of this residue showed that the starting material was absent. The crude product was finely powdered, and mixed with Celite (3.0 g), and the mixture was continuously extracted with benzene for 48 h in a Soxhlet extraction apparatus. Evaporation of the extract to dryness gave a solid, which was recrystallized from acetone–hexane to give a white, crystalline material; yield 0.87 g (37%), m.p. 143–146°. A second recrystallization from acetone–hexane afforded pure material, m.p. 149–151°, $[\alpha]_D^{21}$ +200 ±1° (*c* 1.6, methanol); λ_{max}^{KBr} 3.05 (NH, OH), 5.88 (*N*-trifluoroacetyl carbonyl), 6.46 (NH), 8.55 (CF), 3.46, 6.8, 6.9, 7.3, 7.6, 7.7, 8.0, 8.44, 8.96, 9.2, 9.35, 9.65, 10.07, 10.36, 10.95, 11.2, 11.78, 12.68, 13.15, and 13.7 μm; X-ray powder diffraction data: 14.73 m, 9.21 s, 7.56 vs (3), 6.97 s, 5.96 m, 5.10 vs (2), 4.76 s, 4.51 vs (1), 4.28 s, 4.04 m, 3.78 m, 3.48 vs (3), 3.37 vw, 3.19 m, 2.97 s, 2.82 w, 2.70 s, 2.57 m, 2.39 m, 2.33 m, 2.25 s, 2.17 m, 2.12 vw, 207 w, 2.02 vw, and 1.96 w.

Anal. Calc. for $C_{10}H_{16}F_3NO_5S$: C, 37.62; H, 5.05; N, 4.39; S, 10.04. Found: C, 37.68; H, 5.37; N, 4.54; S, 10.51.

This compound was homogeneous by t.l.c. with ethyl acetate or 3:2 acetone–chloroform as the developer.

Method B. A mixture of ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside[3,4] (**3**, 2.0 g), barium hydroxide octahydrate (15.0 g), and water (100 ml) was boiled under reflux for 24 h. The mixture was cooled, and solid carbon dioxide was added until the solution was neutral to phenolphthalein; Celite (5.0 g) was added, and the mixture was filtered. The filtrate was concentrated to a small volume, and the water remaining was removed by addition and evaporation of absolute ethanol. The residue was extracted with absolute ethanol (100 ml), and the extract was evaporated to a syrup (**4**).

This syrup was dissolved in absolute methanol (25 ml), *S*-ethyl trifluorothioacetate (2 ml) was added, the mixture was kept for 24 h at room temperature and then evaporated, and the residue was extracted with acetone (100 ml). The

extract was evaporated, and the residue was chromatographed with a column (2.3 × 33 cm) of silica gel*, with ethyl acetate as the developer. The first 50 ml of eluate was discarded; the next 1000 ml was collected, and evaporated to yield a white solid, which was recrystallized from acetone–hexane; yield 1.15 g (70%), m.p. 146–148°. A second recrystallization from acetone–hexane afforded pure material, m.p. and m.m.p. with **2** prepared by the procedure described in *Method A*, 149–151°, $[\alpha]_D^{21}$ +201 ±1° (*c* 1.3, methanol). The X-ray powder diffraction data were identical with those for the compound prepared by *Method A*.

Ethyl 3,5,6-tri-O-acetyl-2-deoxy-1-thio-2-(trifluoroacetamido)-α-D-gluco-furanoside (**5**). — Compound **2** (2.0 g) was added to a mixture of acetic anhydride (7 ml) and pyridine (12 ml). After 24 h at room temperature, the solution was poured, with stirring, into ice and water (30 ml), the mixture was extracted with dichloromethane (100 ml), and the extract was washed with water, dried (sodium sulfate), and evaporated to a colorless syrup; this was crystallized from ether–hexane, to give white crystals; yield 2.55 g (91%), m.p. 72–74°, $[\alpha]_D^{21}$ +135 ±1° (*c* 1.7, chloroform); λ_{max}^{KBr} 3.05 (NH), 5.72 (*O*-acetyl carbonyl), 5.85 (*N*-trifluoroacetyl carbonyl), 6.46 (NH), 8.0–9.1, 8.3 (ester), 8.6 (CF), 3.3, 3.45, 6.92, 7.3, 8.4, 9.1, 9.42, 9.63, 10.23, 10.55, 10.75, 11.05, 11.28, 11.46, 11.77, and 13.5 μm; X-ray powder diffraction data: 10.05 vs (1), 8.27 vw, 6.81 vw, 4.96 vs (2), 4.76 m, 4.59 s, 4.38 s, 4.11 s (3), 3.96 w, 3.88 s, 3.74 w, 3.61 s, 3.48 vw, 3.36 vw, 3.25 m, 3.16 m, 2.82 vw, and 2.75 w.

Anal. Calc. for $C_{16}H_{22}F_3NO_8S$: C, 43.14; H, 4.98; N, 3.14; S, 7.20. Found: C, 43.00; H, 5.36; N, 3.36; S, 7.69.

This compound was homogeneous by t.l.c. with 2:1 ether–hexane as the developer.

1-[3,5,6-Tri-O-acetyl-2-deoxy-2-(trifluoroacetamido)-β-D-glucofuranosyl]cytosine (**7**). — Compound **5** (2.0 g) was dissolved in dichloromethane (15 ml), and dry chlorine was passed through the solution for 15 min. Evaporation of the solvent at 20° gave a pale-yellow syrup; this was redissolved in dichloromethane, and a few drops of cyclohexene were added. After evaporation of the solvent at 20°, the resulting syrup was dissolved in chloroform (10 ml), bis(trimethylsilyl)cytosine[6,7] (3.7 g) was added, and the mixture was stirred for a few minutes until homogeneous. The solvent was evaporated, and the residue was heated for 12 min at 130–140° under diminished pressure (water aspirator). After being cooled to room temperature, the crude product was added to 80% aqueous ethanol (50 ml) containing sodium hydrogen carbonate (0.6 g), and the mixture was heated for 15 min at 60°, with stirring. The solvent was evaporated, the residue was extracted with chloroform (200 ml), and the extract was dried (sodium sulfate), and evaporated to dryness. The residue (1.4 g) crystallized slowly from methanol–isopropyl ether; yield 0.27 g (12%), m.p. 257–259°. A second recrystallization from methanol–isopropyl ether afforded pure **7**, m.p. 262–264°; $[\alpha]_D^{21}$ +25 ±1° (*c* 1.1, methanol); λ_{max}^{KBr} 3.1 (NH_2), 5.7–5.8

*Grade 950, 60–200 mesh; Grace Chemical Co. Division of Davison Chemical Co., Baltimore, Md.

(*O*-acetyl and *N*-trifluoroacetyl carbonyl), 6.05–6.15, 6.4, 6.72 (NH, cytosine), 8.1–8.3 (ester), 8.62 (CF), 7.32, 7.8, 8.62, 9.5, 10.5, 10.95, 11.75, 12.0, 12.5, and 14.3 μm; λ_{max}^{EtOH} 206 (ε 20,000), 244 (shoulder, 8,870), and 270 nm (9,020); X-ray powder diffraction data: 10.05 m, 8.51 vs (1), 7.50 m, 6.86 vw, 6.37 s, 5.87 vs, 5.54 vw, 5.23 m, 4.93 vs (3), 4.58 s, 4.36 vs (2), 4.10 s, 3.94 s, 3.73 vs (3), 3.55 m, 3.42 w, 3.31 w, 3.19 m, 3.11 vw, 2.88 s, 2.75 m, 2.62 vw, 2.45 w, 2.33 w, 2.27 w, 2.22 w, 2.12 m, 1.94 w, 1.88 m, and 1.78 w.

Anal. Calc. for $C_{18}H_{21}F_3N_4O_9$: C, 43.73; H, 4.29; N, 11.33. Found: C, 43.61; H, 4.40; N, 11.59.

This compound was homogeneous by t.l.c. with 3:1 ethyl acetate–methanol or 3:1 acetone–chloroform as the developer. T.l.c. of the mother liquors with 3:1 acetone–chloroform as the developer revealed two major, overlapping components (R_F 0.8 and 0.7) and three minor components (R_F 0.45, 0.25, and 0.1). The component having R_F 0.25 corresponded to **7**. The five components were isolated by preparative t.l.c. with 3:1 acetone–chloroform as the developer. Crystallization from methanol–isopropyl ether of the component having R_F 0.25 gave an additional 0.05 g (2.3%) of **7**. The other four components were examined by i.r. and u.v. spectroscopy, but none of them showed absorptions characteristic of cytosine nucleoside derivatives.

*1-(2-Amino-2-deoxy-β-*D*-glucofuranosyl)cytosine sulfate* (**8b**). — Compound **7** (0.30 g) was dissolved in methanol presaturated at 0° with ammonia (50 ml). After 7 days at room temperature, the solution was concentrated to ~5 ml, and ether (60 ml) was added. The resulting, flocculent precipitate was filtered off, and washed with ether (20 ml), to give crude **8a** as amorphous material.

Crude **8a** was dissolved in methanol (10 ml) and 3M sulfuric acid was added; a precipitate formed immediately. Ether (10 ml) was added to ensure complete precipitation, and the precipitate was filtered off, washed with ethanol, and crystallized from methanol; yield 0.19 g (85%), m.p. 248–249° (dec.), $[\alpha]_D^{22}$ +42 ±2° (*c* 0.4, water); o.r.d. spectrum (see Fig. 1): $[M]_{238}^{20}$ +9,000° (peak), $[M]_{238}^{20}$ −13,500 (trough) (*c* 0.01, water); λ_{max}^{KBr} 3.0–3.1 (OH), 3.25–3.4 (NH_3^+), 5.8, 6.05, 6.25, 6.52 (cytosine), 7.06, 7.48, 7.58, 8.05, 8.6, 9.0–9.2, 9.62, 10.3, 11.25, 11.95, 12.8, and 13.15 μm; $\lambda_{max}^{H_2O}$ 202 (ε 15,700), 230 (shoulder, 7,440), and 271 nm (8,700); $\lambda_{max}^{0.1MHCl}$ 212 (ε 10,700) and 278 nm (13,900); X-ray powder diffraction data: 10.34 vs (2), 7.79 s, 6.76 vw, 6.37 m, 5.63 s, 5.14 s, 4.78 s, 4.45 vs (1), 4.13 s, 3.88 s, 3.76 s, 3.48 vs (3), 3.36 m, 3.25 m, 3.16 w, 3.10 w, 3.03 m, 2.92 m, 2.83 s, 2.75 w, 2.71 w, 2.64 m, 2.57 s, 2.43 m, 2.36 m, 2.29 w, 2.23 s, 2.15 m, 2.11 vw, 2.06 w, 2.00 w, and 1.96 s.

Anal. Calc. for $C_{10}H_{18}N_4O_9S$: C, 32.43; H, 4.90; N, 15.13; S, 8.66. Found: C, 32.32; H, 5.20; N, 15.23; S, 8.70.

*1-[3,5,6-Tri-O-acetyl-2-deoxy-2-(trifluoroacetamido)-β-*D*-glucofuranosyl]thymine* (**9**). — Compound **5** (2.0 g) was dissolved in dichloromethane (15 ml), and chlorine was passed through the solution for 10 min. After an additional 10 min, the solution was evaporated to a syrup; this was redissolved in dichloromethane (10 ml) and a few drops of cyclohexene were added. After evaporation of the solvent, bis(trimethylsilyl)thymine[6,7] (2.5 g) and dichloromethane (5 ml) were added, and the mixture

was stirred until homogeneous. The solvent was evaporated, and the residue was heated for 10 min at 130–140° under diminished pressure (water aspirator). The product was cooled to room temperature, and 80% aqueous methanol (25 ml) was added. After the mixture had been thoroughly stirred, the solvent was evaporated, and the residue was extracted with hot chloroform (120 ml). The extract was washed, dried (sodium sulfate), and evaporated to dryness, giving a glass (2.2 g) which crystallized slowly from dichloromethane–isopropyl ether; yield 1.15 g (52%), m.p. 205–208°. A second recrystallization from dichloromethane–isopropyl ether afforded pure material, m.p. 211–212°, $[\alpha]_D^{21}$ −20 ±1° (*c* 1.2, chloroform); λ_{max}^{KBr} 3.0–3.1 (NH), 5.75 (*O*-acetyl and *N*-trifluoroacetyl carbonyl), 5.95, 6.1, 6.5, 6.8 (NH, thymine), 8.1–8.3 (ester), 8.6 (CF), 7.1, 7.4, 9.2, and 9.8 μm; λ_{max}^{EtOH} 210 (ε 10,600) and 266 nm (9,280); X-ray powder diffraction data: 10.92 vs (2), 8.67 vs (3), 7.03 s, 5.68 w, 5.47 w, 5.22 s, 4.85 s, 4.58 s, 4.35 m, 4.15 s, 3.92 s, 3.69 vs (1), and 3.52 m.

Anal. Calc. for $C_{19}H_{22}F_3N_3O_{10}$: C, 44.80; H, 4.35; N, 8.25. Found: C, 44.40; H, 4.39; N, 8.52.

*1-(2-Amino-2-deoxy-β-*D*-glucofuranosyl)thymine hydrochloride* (**10b**). — Compound **9** (0.4 g) was dissolved in methanol presaturated at 0° with ammonia (50 ml). After 7 days at room temperature, the solution was concentrated to ~5 ml, and ether (50 ml) was added. The resulting, flocculent precipitate (**10a**) was filtered off, and washed with ether.

Crude **10a** was dissolved in methanol (10 ml), and 2M hydrochloric acid (0.5 ml), was added. Several additions and evaporations of ethanol were made in order to remove the excess of hydrochloric acid. The residue crystallized from methanol–ethanol–ether; yield 0.23 g (83%), m.p. 289–291° (dec.), $[\alpha]_D^{21}$ −1.5 ±1° (*c* 1.1, water); o.r.d. spectrum: $[M]_{285}^{23}$ +3,100° (peak), $[M]_{250}^{23}$ −8,000° (trough), (*c* 0.01, water); λ_{max}^{KBr} 2.9–3.1 (OH), 3.2–3.4 (NH_3^+), 5.95, 6.1, 6.85 (thymine), 7.3, 7.7, 7.9, 9.3, 10.0, 10.8, and 11.4 μm; λ_{max}^{H2O} 209 (ε 8,580) and 269 nm (9,720); X-ray powder diffraction data: 12.28 m, 8.59 m, 6.19 s, 5.79 vs (2), 5.54 m, 5.10 s, 4.35 vs (1), 4.17 m, 4.04 s, 3.72 vs (3), 3.61 s, 3.49m, 3.33 m, 3.12 s, 3.02 m, 2.92 s, and 2.77 s.

Anal. Calc. for $C_{11}H_{18}ClN_3O_6$: C, 40.87; H, 5.57; N, 12.92. Found: C, 40.83; H, 5.29; N, 13.28.

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